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10/551,603	01/20/2006	Thomas C. Schulz	18377-0067	8027

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	PAPER NUMBER
1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,603	SCHULZ ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *07 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18 and 31* is/are pending in the application.

4a) Of the above claim(s) *10-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *9/30/2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/30/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response of May 7, 2007, to the Restriction Requirement dated April 9, 2007 has been entered. No claims have been amended, cancelled or newly added. Claims 1-18 and 31 are pending in the application.

Election/Restrictions

Applicant's election of Group I (claims 1-9 and 31) with traverse, drawn to a human pluripotent embryonic stem cell culture, wherein the cells of the culture do not express SSEA1, express SSEA3, SSEA4, Oct4, Tra-1-60, Tra-1-80 and nestin, is acknowledged. Applicants' species election of trisomy of chromosome 17, also with traverse, is further acknowledged. The traversal is on the basis that the two groups share the same technical feature that is a human embryonic stem cell culture, wherein the cells express nestin substantially uniformly. Applicants' arguments have been fully considered, but are not found to be persuasive, because as set forth in the proceeding discussion, when the instant claims are interpreted in view of the as filed specification, it is apparent that a sub-population of cells in the human pluripotent stem cell culture that do not express SSEA1, express nestin only after embryoid body formation, and wherein the cells are differentiating or committed to a cell lineage prior to the neuroprogenitor stage, and thus are no longer pluripotent. Therefore, the restriction between Groups I and II is maintained. Additionally, as indicated on page 3 of the restriction requirement dated 4/9/2007, any nonelected processes of making and/or using an allowable product will be considered for rejoinder following the practice set forth in MPEP § 821.04(b).

Applicants' traversal of the species requirement is on the basis that examination of the different chromosomal trisomies would not place a serious burden because of their close technological relationship and sufficiently small number. Such is not found persuasive, because Applicants have relied on U.S. restriction practice in a case where restriction was properly applied under rules for Unity of Invention. While examination burden was not the grounds for restriction in the instant case, Applicants should note that a search of trisomy 1 is not co-extensive with a search of trisomy 17, for example.

Claims 10-18 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. The requirement for restriction is deemed proper, maintained and hereby made FINAL.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Applicant timely responded to the restriction (election) requirement in the Paper filed May 7, 2007. Claims 1-9 and 31 are currently under examination.

Priority

The disclosure of the prior-filed Provisional Application, No. 60/459,090, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Specifically, the '090 Application does not include Example 19 or a disclosure of the abnormal karyotypes in bulk passaged HESCs. Therefore, claims 3-9 drawn to these limitations are denied benefit of priority to the 60/459,090 application.

Therefore, the effective filing date of the instant application with regards to claims 3-9 is the filing date of PCT/US04/10121, filed 3/31/2004.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is unclear. Claim 1 is directed to a human pluripotent embryonic stem cell culture, wherein the cells of the culture do not express SSEA1, but express SSEA3, SSEA4, Oct4, Tra-1-60, Tra-1-80 and nestin. However, when interpreted in view of the instant specification, it is apparent that cells expressing said markers are differentiating cells present in embryoid bodies that are committed to the neural differentiation path and are thus no longer pluripotent cells. Further, as the claim is directed to a mixed culture of cells undergoing differentiation, it is unclear which cell types are actually being claimed. Thus the metes and bounds of "the cells" is the stem cell culture remains undefined.

Claim 31 is similarly unclear, as the claim is directed to a human pluripotent cell produced by a method of mixed cell culture wherein the cells do not express SSEA1, but express SSEA3, SSEA4, Oct4, Tra-1-60, Tra-1-80 and nestin.

Claims 2-9 depend from base claim 1, and are therefore included in the rejection.

Claim Rejections - 35 USC § 112-Lack of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1-9 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification is not enabling for a human pluripotent stem cell culture, wherein the cells of the culture do not express SSEA1, express SSEA3, SSEA4, Oct4, Tra-1-60, Tra-1-80, and express nestin substantially uniformly, as claimed.

This rejection is based on several issues relating to the absence of an enabling disclosure for the claimed cells of a human stem cell culture that retain pluripotency while expressing cell surface markers for SSEA3, SSEA4, Oct4, Tra-1-60, Tra-1-80, and nestin. The deficiency was identified by the Office after analysis of the disclosure provided in the instant application. In determining whether Applicant's claims are enabled, it must be found that one of skill in the art

at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404:

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The Office has analyzed the specification in direct accordance to the factors outlined in *In re Wands*. MPEP § 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection."

The instant claims encompass a culture of human pluripotent embryonic cells that do not express SSEA1, but express SSEA3, SSEA4, Oct4, Tra-1-60, Tra-1-80, and express nestin substantially uniformly. The term "substantially uniformly" refers to the expression pattern of a cellular marker when most of the cells of a colony of cells express the marker (lines 17-20, p. 18).

The instant specification discloses that the invention encompasses providing a human cell culture enriched in neural cells, comprising the formation of an embryoid body that comprises a human pluripotent cell culture that expresses SSEA3, SSEA4, Oct4, Tra-1-60, Tra-1-80, and express nestin substantially uniformly (paragraphs [061], p. 19). Example 6 of the specification describes cell culture conditions for bulk passaged human embryonic stem cell (HESCs), disclosing that undifferentiated HESCs were selected by magnetic sorting using anti-SSEA4 antibody (p. 54). The cells were used for generation of embryoid bodies by plating HESCs on feeder layers that were 0-6 hours old, and the HESC colonies formed exhibited a "crater" in the central region of the colony, within 3 to 5 days. Cells within the crater expressed the pluripotent marker Oct4, at a reduced level compared to the surrounding ring of HESCs, indicating that they were a novel, partially differentiated cell type (paragraph [0145], pp. 55-56).

Example 11 describes immunostaining of the embryoid body cells of Example 6, stating that the HESCs contained the expected pattern of marker expression for undifferentiated pluripotent cells: $SSEA4^+$, $Oct4^+$, Tra-1 -60^+, Tra-1-81^+, $SSEA3^+$, and $SSEA1^-$, but also expressed nestin (paragraph [0176], p. 65), further stating that this bulk passaged population could be a downstream cell population with some pre-neural stem cell gene expression characteristics (lines 8-10, p. 66).

Therefore, it is apparent that the embryoid body cells analyzed for expression of the various cell surface markers are a mixed cell population comprising a continuum of differentiation states. Moreover, the specification is silent on the pluripotency of the cells present in the differentiating embryoid body cells, as the cells were not demonstrated to retain the ability to differentiate into all cell lineages, or the purification of a single population of cells exhibiting the claimed marker signature.

In a review of conditions used in ES cell differentiation towards a neural fate, Lang et al. (J. Neurosci. Res. 76:184-192), state that the formation of neural lineages in embryoid bodies has not been analyzed in detail, but it seems to recapitulate events in the embryo with a temporal progression between intermediate cell populations of progressively restricted developmental potential (first column, p. 186). Thus, it is apparent that differentiating cells in an embryoid body are restricted in developmental potential and may not be correctly characterized as pluripotent.

As a separate issue, the instant claims are further directed to a human pluripotent embryonic stem cell culture wherein a majority of the cells have an abnormal karyotypic abnormality, that is a trisomy of chromosome 17. Example 19 teaches that bulk passaging cell cultures with collagenase/trypsin and dissociating them to an essentially single cell culture appears to lead to the development of an abnormal phenotype (p. 78). However the specification is silent on the pluripotency of abnormal cells. The post-filing art of Mandal et al. (U.S. Patent Publication No.: 2006/0286544; filed May 17, 2006) describes the purification of human ES cell populations that are $SSEA1^-$, TRA-1-60^+, TRA-1-81^+ and $Oct4^+$, and retain the ability to differentiate into cell and tissue types derived from all three embryonic germ layers (endoderm, mesoderm, and ectoderm), but have normal karyotypes (Abstract). The authors observe that the genetic stability of human ES cells can be assessed and normally, human ES cells maintain a stable karyotypes, but that with increased passaging, the cells show abnormal karyotypes

including trisomies of chromosomes 12-17 (paragraph [0018], first column, p. 3). As cells carrying abnormal karyotypes are to be avoided in the potential use of these cells as therapeutics, the usefulness of the instantly claimed abnomal ES cells remains unclear. Please note "case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970.

Therefore, in view of the aforementioned deficiencies and the absence of any guidance in the disclosure of the instant application regarding the use of the abnormal human ES cells, the person of skill in the art would have to perform additional undue experimentation to isolate and purify a human ES cell that is $SSEA1^-$, $SSEA3^+$, $SSEA4^+$, $Oct4^+$, $TRA\text{-}1\text{-}60^+$, $TRA\text{-}1\text{-}81^+$, $nestin^+$ and retains the ability to differentiate into cell and tissue types derived from all three embryonic germ layers.

The guidance provided by the specification amounts to an invitation for the skilled Artisan to try and follow the disclosed instructions to use the claimed invention. At the time of the instant invention, the skilled artisan not have been able to predict without undue experimentation whether the human ES culture contained cells that are at once $SSEA1^-$, $SSEA3^+$, $SSEA4^+$, $Oct4^+$, $TRA\text{-}1\text{-}60^+$, $TRA\text{-}1\text{-}81^+$, $nestin^+$ and pluripotent.

Therefore, in view of the lack of enabling disclosure for the pluripotent HESCs, it would have required undue experimentation for one of skill in the art to use said model. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects

for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

To the extent that the instant claims encompass a mixed population of cultured human embryonic stem cells undergoing differentiation toward a neural fate in an embryoid body, the following rejection over the prior art is applicable.

Claims 1-2 and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Carpenter (U.S. Patent No.: 6,833,269; filed May 31, 2001).

Claim 31 is drawn to a human pluripotent cell produced by the method of claim 10 and is thus a product by process claim.

MPEP 2112.01 states: "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best,* 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977)." MPEP 2113 further states: "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Carpenter teaches populations of human embryonic stem cells and neural progenitor cells by culturing, expanding and differentiating embryonic stem cells into a variety of different neural phenotypes in a cocktail of growth conditions (Abstract). Specifically, The cells are expanded by serial passaging, removed and used in formation of embryoid bodies (column 21). Further teaching, primate ES cells express stage specific embryonic antigens SSEA 3 and 4 and markers designated Tra-1-60 and Tra-1-81, and that the differentiation of pPS (primate pluripotent stem) cells *in vitro* results in the loss of SSEA-4, Tra-1-60 and Tra-1-80 expression and increased expression of SSEA-1 (lines 44-53; column 11). Carpenter additionally teaches that the Oct-4 marker is characteristic of undifferentiated hES cells and Nestin is characteristic of neural precursor cells (lines 35-43, column 14). In Example 5, Carpenter describes the differentiation of

embryoid body cells and the identification of neural precursors as cells positive for nestin staining and the absence of lineage specific differentiation markers (lines 41-46, column 28, Table 6 and claim 1). In column 20, lines 39-42, Carpenter teaches single cell suspension of neural stem cells that may be transplanted.

Therefore by teaching all the limitations of claims 1-2 and 31, Carpenter anticipates the instant invention as claimed.

Claim 31 is rejected under 35 U.S.C. 102(b) as being anticipated by Odorico et al. (Stem Cells 19:193-204; 2001).

Odorico et al. teach human pluripotent stem cells that can differentiate into derivatives of all three embryonic germ layers (Abstract). Additionally teaching, human ES cells express stage-specific embryonic antigens 3 and 4 (SSEA-3 and SSEA-4), high molecular weight glycoproteins TRA-1-60 and TRA-1-81. In the legend of Figure 2, the authors teach that in suspension culture, human ES cells differentiate to embryoid bodies or multicellular aggregates and can further differentiate into a variety of cell types including neural cells (panel C, p. 196). Therefore, each and every element and limitation of claim 31, the present invention is anticipated and effectively addressed by Odorico et al. The examiner further maintains that the office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of factual evidence to the contrary, the burden is upon the applicant to prove that the claimed products are **functionally different** than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips,* 28 USPQ 1302, 1303 (BPAI 1993), *In re Best,* 562, F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray,* 10 USPQ2d 1922, 1923 (BPAI 1989). The claiming of a new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977); *In re Spada,* 15 USPQ2d 1655, Federal Circuit, 1990. See also MPEP § 2112.01 with regard to inherency and product-by-process claims.

Conclusion

Claims 1-9 and 31 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is (571) 272-3311. The examiner can normally be reached on 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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